

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: AOKI et al.) Examiner: A. Gupta
) (parent app.)
Serial Number: Pending)
) Art Unit: 1653
Filed: Herein) (parent app.)
)
For: METHOD FOR TREATING PAIN)
WITH BOTULINUM TOXIN TYPE B) Irvine, California

Assistant Commissioner of Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

I. Introduction

This application is a divisional of pending application serial number 09/490,756, filed January 24, 2000, which is a divisional of application serial number 08/627,118, filed April 3, 1996, which is a continuation of application serial number 08/173,966, filed December 28, 1993, now abandoned.

II. Amendments to the Specification

The title of the application has been replaced by a title more descriptive of the claimed subject matter and a cross reference to the parent patent applications has been added to page one of the specification.

III. New Claims 21-52

This divisional application cancels claims original 1-20 and adds new claims 21-52 by this preliminary amendment. All of the new claims 21-52 are supported by the original specification as set forth below.

Generally, use of botulinum toxin type B to treat pain associated with a muscle disorder is supported by the four Examples 7 to 10 on pages 17 to 19 of the specification which disclose use of botulinum toxin type B to treat various types of muscle spasm pain.

Claims 21 is supported by at least: (1) page 1, lines 9-11 of the specification ("the present invention provides methods useful in relieving pain related to muscle activity or contracture"); (2) page 7, lines 11-13 of the specification ("preferably, the toxin is administered by means of intramuscular injection directly into a local area, such as a spastic muscle"); (3) page 8, lines 12-14 of the specification ("The dose of toxin administered to the patient will depend upon the severity of the condition; e.g., the number of muscle groups requiring treatment"); (4) page 17-18, Example 7, page 18, Example 8, pages 18-19, Example 9, and page 19, Example 10 of the specification. Note that each of these four Examples is entitled, ("The Use of Botulinum toxin types A-G in the Treatment of Muscle Spasms and Control of Pain Associated with Muscle Spasms..."); (5) and original claims 6, 10 and 12 (pain from smooth muscle disorders), as well as original claims 14 (muscle spasm pain) and 18 (pain due to arthritic muscle contraction).

Thus, the original specification (including the original claims) amply support a claim directed to use of botulinum toxin type B to treat a painful muscle disorder.

Claim 22 is supported by at least (1) page 1, lines 9-14 of the specification ("the present invention provides methods useful in relieving pain related to...muscle spasm...(and)...pain related to spasticity"); (2) Example 6-10, on

pages 17-19, as all of these five examples relate to (see the title of each example) "Muscle Spasms"). Note that Example 10 at the top of page 19 additionally refers to "Spasticity Conditions.", and; (3) original claims 6, 8, 10, 12, 14, 17 and 19, all of which relate to "spasms."

Claim 23 is supported by at least Example 10 on page 19 of the specification (post stroke or cerebral vascular event").

Claim 24 is supported by at least Example 10 on page 19 of the specification ("Traumatic Brain Injury").

Claim 25 is supported by at least Example 10 on page 19 of the specification ("Spinal Cord Injury").

Claim 26 is supported by at least: (1) page 1, lines 9-13 of the specification ("the present invention provides methods useful in relieving pain related to...muscle spasm such as Temporomandibular Joint Disease"), and; (2) Example 7 on pages 17-18 of the specification ("Temporal Mandibular Joint Disorders").

Claim 27 is supported by at least: (1) page 4, lines 29-30 of the specification ("the present invention provides a method for relieving pain, associated with muscle contractions..."); (2) page 4, line 34 ("a method for treating smooth muscle disorders"), and; (3) and Examples 9 on pages 18-19 of the specification (which example refers to "...Control of Pain Associated with Muscle Spasms in Smooth Muscle Disorders...").

Claim 28 is supported by at least: (1) Example 6 on page 17 of the specification ("constricted pyloric valve"), and; (2) original claim 7, which relates to "pain associated with the smooth muscle of a pyloric valve.

Claim 29 is supported by at least: (1) Example 9 on page 18 of the specification (note disclosure in this example 9 of "spastic colitis and "pain associated with spastic colon"), and; (2) original claims 11 and 13 (lower colon spasms).

Claim 30 is supported by at least (1) page 4, lines 34-35 ("smooth muscle disorders including, but not limited to spasms..."); (2) Example 6 ("...Spasms in Smooth Muscle..."); (3) Example 9 ("...Spasms in Smooth Muscle..."); and; (4) original claims 6, 8, 10 and 12 all of which relate to smooth muscles spasms.

Claim 31 is supported by at least (1) page 4, line 34 continuing to page 5, line 2 ("smooth muscle disorders including, but not limited to spasms...in the gastrointestinal system"); (2) Example 6 on page 17 ("...Spasms in Smooth Muscle...of the Gastrointestinal System"); (3) Example 9 on 18 ("...Control of Pain Associated with Muscle Spasms in Smooth Muscle Disorders Such as Gastrointestinal Muscles"); and; (4) original claims 6, 8, 10 and 12 all of which relate to spasms in gastrointestinal muscles.

Claim 32 is supported by at least: (1) Example 9 on page 18 of the specification (note disclosure in this example 9 of "spastic colitis and "pain associated with spastic colon"), and; (2) original claims 11 and 13 (lower colon spasms).

Claim 33 is supported by at least: (1) page 4, line 29, continuing to page 5, line 1-30 of the specification ("the present invention provides ...a method for treating...spasms in the sphincter of the cardiovascular arteriole..."; (2) Example 6 on page 17 of the specification ("...Smooth Muscle Disorders Such As Sphincters of the Cardiovascular Arteriole..."), and; (3) original claims 6 and 8.

Claim 34 is supported by at least (1) page 4, line 34 continuing to page 5, line 2 ("smooth muscle disorders including, but not limited to spasms...in the

gastrointestinal system"); (2) Example 6 on page 17 ("...Spasms in Smooth Muscle...of the Gastrointestinal System"); (3) Example 9 on 18 ("...Control of Pain Associated with Muscle Spasms in Smooth Muscle Disorders Such as Gastrointestinal Muscles"); and; (4) original claims 6, 8, 10 and 12 all of which relate to spasms in gastrointestinal muscles or to spasms in sphincters of the gastrointestinal system.

Claim 35 is supported by at least (1) page 4, line 34 continuing to page 5, line 2 ("smooth muscle disorders including, but not limited to spasms...in the urinary system"); (2) Example 6 on page 17 ("...Spasms in Smooth Muscle...of the Urinary" System), and; (3) original claims 6 and 8 both of which relate to spasms in urinary system muscles or to spasms in sphincters of the urinary system.

Claim 36 is supported by at least (1) page 4, line 34 continuing to page 5, line 2 ("smooth muscle disorders including, but not limited to spasms in the sphincter of the...gall bladder"); (2) Example 6 on page 17 ("...Spasms in Smooth Muscle...of Gall Bladder"), and; (3) original claims 6 and 8 both of which relate to spasms in gall bladder system muscles or to spasms in sphincters of the gall bladder.

Claim 37 is supported by at least (1) page 4, line 34 continuing to page 5, line 2 ("smooth muscle disorders including, but not limited to spasms in the sphincter of the...rectum"); (2) Example 6 on page 17 ("...Spasms in Smooth Muscle...of Rectal" System and Example 9 on page 18 ("Injection is to the rectum") and; (3) original claims 6, 8, 10 and 12, all of which relate to spasms in rectal muscles or to spasms in rectal sphincters.

Claim 38 is supported by at least (1) page 1, lines 4-15 of the specification ("...the present invention provides methods useful in relieving pain related to...sports injuries..."); (2) page 9, lines 13-14 ("...relief of pain associated with sports injuries..."), and; (3) Example 8 on page 18 ("...Control of Pain Associated

with Muscle Spasms in Conditions Secondary to Sports Injuries.”), and; (3) original claims 14-16 which relate to “relieving pain associated with muscle spasms in conditions secondary to sports injuries....”

Claim 39 is supported by at least (1) Example 8 on page 18 (“...Control of Pain Associated with Muscle Spasms in Conditions Secondary to Sports Injuries ... (upon) severe cramping in thigh...”), and; (3) original claim 17.

Claim 40 is supported by at least (1) page 1, lines 4-15 of the specification (“...the present invention provides methods useful in relieving pain related to...contractures in arthritis...”); and (2) original claim 18.

Claim 41 is supported by at least page 1, lines 4-15 of the specification (“...the present invention provides methods useful in relieving pain related to...low back pain...”).

Claim 42 is supported by at least page 1, lines 4-15 of the specification (“...the present invention provides methods useful in relieving pain related to...myofascial pain...”).

Claim 43 is supported by at least (1) page 1, lines 9-14 of the specification (“the present invention provides methods useful in relieving pain related to...muscle spasm...(and)...pain related to spasticity”); (2) Example 6-10, on pages 17-19, as all of these five examples relate to (see the title of each example “Muscle Spasms”). Note that Example 10 at the top of page 19 additionally refers to “Spasticity Conditions.”, and; (3) original claims 6, 8, 10, 12, 14, 17 and 19, all of which relate to “spasms.”

Claim 44 is supported by at least page 8, lines 24-26 of the specification.

Claim 45 is supported by at least page 7, lines 11-13 of the specification. Additionally, claim 48 is supported by at least page 9, lines 21-23 of the specification which states that: "In each of the following examples, appropriate areas of each patient are injected with a sterile solution containing the confirmation of Botulinum toxin" (see also page 9, line 29 "injecting the muscle"). Additionally, page 7, lines 11-15 discloses two methods of "injection" as the preferred administration route for the toxin and page 7, line 34 of the specification states that the toxin is administered by injection.

Claim 46 is supported by at least Examples 1 to 11 on pages 10 to 20 of the specification.

Claim 47 is supported by at least page 1, lines 26-29 and page 3, lines 9-11 of the specification.

Claim 48 is a picture claim which incorporates the limitations of claims 21, 22, 45 and 47.

Claim 49 is supported by at least:

- (a) Example 7 on pages 17 and 18 of the specification which discloses treatment of pain in the temporal mandibular joint (i.e. jaw muscles);
- (b) Example 8 on page 18 which discloses treatment of pain in sports injured muscles, including the thigh muscles;
- (c) Example 9 on page 19 which discloses treatment of pain in hand, wrist, forearm and leg muscles, and;
- (d) Example 10 on page 19 which discloses treatment of throat muscles.

Thus, treatment of pain in essentially every major peripheral or non-GI tract skeletal muscle is disclosed by the original specification and claim 49 is therefore supported by the specification.

Claim 50 is supported by at least (1) page 4, lines 34-35 ("smooth muscle disorders including, but not limited to spasms..."); (2) Example 6 ("...Spasms in Smooth Muscle..."); (3) Example 9 ("...Spasms in Smooth Muscle..."); and; (3) original claims 6, 8, 10 and 12 all of which relate to smooth muscles spasms.

Claim 51 is a picture claim which incorporates the limitations of claims 21, 41, 45, and 47.

Claim 52 is a picture claim which incorporates the limitations of claims 21, 22, 23, 45 and 47.

IV. Claims 21-52 are in Condition for Allowance

Enclosed is a copy of the February 8, 2001 declaration of Mitchell Brin, which declaration was submitted in co-pending application serial number 09/490,756 with applicants response dated February 16, 2001 in co-pending application serial number 09/490,756.

Paragraph 6 of the Brin declaration states: "As of the April 25, 1991 date of the Jankovic reference it was completely unknown as to whether or not botulinum toxin type B would have any therapeutic efficacy in humans. Indeed, as far as I am aware, the first reported use of type B botulinum toxin in humans did not occur until 1995."

Additionally, paragraph 8 of the Brin declaration states: "In my opinion, prior to December 28, 1993, it would have been foolhardy and dangerous to use botulinum toxin type B to treat patients with dystonia, such as cervical dystonia, in light of the complete lack of clinical experience with the type B toxin as of that date."

The Brin declaration is submitted herein as evidence that the claims in this application are in condition for allowance. In other words, since there had been no use of botulinum toxin type B to treat any disease condition prior to the effective filing date of the present application (December 23, 1993) and based upon the additional evidence presented by the Brin declaration, the present claims 21-52 being directed to use of a botulinum toxin type B to treat pain associated with a muscle disorder are free of the art and in condition for allowance.


V. Co-Pending Application

Applicants wish to bring to the attention of the examiner co-pending application serial number 09/487,470, filed January 19, 2000 entitled Method for Treating Pain Associated with a Muscle Disorder.

VI. Conclusion

Examination and allowance of claims 21-52 is requested.

Respectfully Submitted,


Stephen Donovan
Registration Number 33,433

Date: June 18, 2001

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CERTIFICATE OF EXPRESS MAIL UNDER 37 C.F.R. § 1.10

I hereby certify that the Transmittal Letter, the divisional patent application, preliminary amendment, and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date June 18, 2001 in an envelope as "Express Mail Post Office to Addressee" Mailing Label number EL385558745US addressed to Box Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231

Susan Bartholomew
Name of person mailing paper


Signature of person mailing paper

Date: June 18, 2001

**PLEASE REPLACE PAGE 1 OF THE SPECIFICATION BY THE FOLLOWING
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METHOD FOR TREATING PAIN WITH BOTULINUM TOXIN TYPE B

CROSS REFERENCE

This application is a divisional of application serial number 09/490,756, filed January 24, 2000, which is a divisional of serial number 08/627,118, filed April 3, 1996, which is a continuation serial number 08/173,996, filed December 28, 1993, now abandoned.

FIELD OF THE INVENTION

The present invention provides novel methods for treating various disorders and conditions, with Botulinum toxins. Importantly, the present invention provides methods useful in relieving pain related to muscle activity or contracture and therefore is of advantage in the treatment of, for example, muscle spasm such as Temporomandibular Joint Disease, low back pain, myofascial pain, pain related to spasticity and dystonia, as well as sports injuries, and pain related to contractures in arthritis.

BACKGROUND OF THE INVENTION

Heretofore, Botulinum toxins, in particular Botulinum toxin type A, has been used in the treatment of a number of neuromuscular disorders and conditions involving muscular spasm; for example, strabismus, blepharospasm, spasmodic torticollis (cervical dystonia), oromandibular dystonia and spasmodic dysphonia (laryngeal dystonia). The toxin binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. This results in local paralysis and hence relaxation of the muscles afflicted by spasm.

For one example of treating neuromuscular disorders, see U.S. Patent No. 5,053,005 to Borodic, which suggests treating curvature of the juvenile

**THE FOLLOWING PAGES SHOWS A MARKED UP VERSION OF PAGE 1 OF
THE SPECIFICATION**

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METHOD FOR TREATING PAIN WITH USE OF BOTULINUM TOXIN TYPE
~~BFOR TREATING VARIOUS DISORDERS AND CONDITIONS AND~~
ASSOCIATED PAIN

CROSS REFERENCE

This application is divisional of application serial number 09/490,756, filed January 24, 2000, which is a divisional of serial number 08/627,118, filed April 3, 1996, which is a continuation of serial number 08/173,996, filed December 28, 1993, now abandoned.

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For one example of treating neuromuscular disorders, see U.S. Patent No. 5,053,005 to Borodic, which suggests treating curvature of the juvenile

**PLEASE REPLACE THE CLAIMS BY THE
FOLLOWING UNMARKED VERSION OF THE CLAIMS**

21. A method for treating pain associated with a muscle disorder, the method comprising the step of administering an effective amount of a botulinum toxin type B to a patient, thereby reducing pain associated with a muscle disorder.

22. The method of claim 21, wherein the muscle disorder is a muscle spasm or a spasticity condition.

23. The method of claim 22, wherein the spasticity condition is secondary to a stroke or a cerebral vascular event.

24. The method of claim 22, wherein the spasticity condition is secondary to a traumatic brain injury.

25. The method of claim 22, wherein the spasticity condition is secondary to a spinal cord injury.

26. The method of claim 22 wherein the muscle spasm is associated with Temporomandibular Joint Disorder.

27. The method of claim 21, wherein the pain is associated with a smooth muscle disorder.

28. The method of claim 27, wherein the smooth muscle disorder is a constricted pyloric valve.

29. The method of claim 27 wherein the smooth muscle disorder is spastic colitis.

30. The method of claim 27, wherein the smooth muscle disorder is a spasmodic muscle.

31. The method of claim 30, wherein the spasmodic muscle is in the gastrointestinal system.

32. The method of claim 30, wherein the spasmodic muscle is in the colon.

33. The method of claim 30, wherein the spasmodic muscle is a sphincter of a cardiovascular arteriole.

34. The method of claim 30, wherein the spasmodic muscle is a sphincter in the gastrointestinal system.

35. The method of claim 30, wherein the spasmodic muscle is a sphincter in the urinary system.

36. The method of claim 30, wherein the spasmodic muscle is a sphincter of the gall bladder.

37. The method of claim 30, wherein the spasmodic muscle is a rectal sphincter.

38. The method of claim 22, wherein the pain is associated with a muscle spasm in a condition secondary to a sports injury.

39. The method of claim 38, wherein the muscle spasm occurs in the patient's thigh and the botulinum toxin is administered into the thigh.

40. The method of claim 21, wherein the pain is related to contractures in arthritis.

41. The method of claim 21, wherein the pain is lower back pain.
42. The method of claim 21, wherein the pain is myofascial pain.
43. The method of claim 21, wherein the pain is related to spasticity.
44. The method of claim 21, wherein the botulinum toxin is administered in an amount of at least about 1,000 units.
45. The method of claim 21, wherein the botulinum toxin is administered by intramuscular injection.
46. The method of claim 21, wherein the botulinum toxin is administered to a human patient.
47. The method of claim 21, wherein the muscle disorder is a cholinergic influenced muscle disorder.
48. A method for relieving pain associated with a muscle spasm, the method comprising the step of intramuscular injection to a cholinergic influenced spasmodic muscle of a patient of a therapeutically effective amount of botulinum toxin type B in order to relieve pain associated with the spasmodic muscle.
49. The method of claim 48 wherein the spasmodic muscle is a peripheral skeletal muscle outside the gastrointestinal tract.
50. The method of claim 48, wherein the spasmodic muscle is a smooth muscle.
51. A method for treating lower back pain, the method comprising the step of intramuscular injection to a cholinergic influenced muscle of a patient of a

therapeutically effective amount of botulinum toxin type B, thereby reducing a lower back pain.

52. A method for treating post stroke spasticity pain, the method comprising the step of intramuscular injection to a cholinergic influenced muscle of a patient of a therapeutically effective amount of botulinum toxin type B, thereby reducing a post stroke spasticity pain.

MARKED UP VERSION OF THE CLAIMS

Cancel claims 1-20.

Please add the following new claims:

21. A method for treating pain associated with a muscle disorder, the method comprising the step of administering an effective amount of a botulinum toxin type B to a patient, thereby reducing pain associated with a muscle disorder.

22. The method of claim 21, wherein the muscle disorder is a muscle spasm or a spasticity condition.

23. The method of claim 22, wherein the spasticity condition is secondary to a stroke or a cerebral vascular event.

24. The method of claim 22, wherein the spasticity condition is secondary to a traumatic brain injury.

25. The method of claim 22, wherein the spasticity condition is secondary to a spinal cord injury.

26. The method of claim 22 wherein the muscle spasm is associated with Temporomandibular Joint Disorder.

27. The method of claim 21, wherein the pain is associated with a smooth muscle disorder.

28. The method of claim 27, wherein the smooth muscle disorder is a constricted pyloric valve.

29. The method of claim 27 wherein the smooth muscle disorder is spastic colitis.

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35. The method of claim 30, wherein the spasmodic muscle is a sphincter in the urinary system.

36. The method of claim 30, wherein the spasmodic muscle is a sphincter of the gall bladder.

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41. The method of claim 21, wherein the pain is lower back pain.

42. The method of claim 21, wherein the pain is myofascial pain.

43. The method of claim 21, wherein the pain is related to spasticity.

44. The method of claim 21, wherein the botulinum toxin is administered in an amount of at least about 1,000 units.

45. The method of claim 21, wherein the botulinum toxin is administered by intramuscular injection.

46. The method of claim 21, wherein the botulinum toxin is administered to a human patient.

47. The method of claim 21, wherein the muscle disorder is a cholinergic influenced muscle disorder.

48. A method for relieving pain associated with a muscle spasm, the method comprising the step of intramuscular injection to a cholinergic influenced spasmodic muscle of a patient of a therapeutically effective amount of botulinum toxin type B in order to relieve pain associated with the spasmodic muscle.

49. The method of claim 48 wherein the spasmodic muscle is a peripheral skeletal muscle outside the gastrointestinal tract.

50. The method of claim 48, wherein the spasmodic muscle is a smooth muscle.

51. A method for treating lower back pain, the method comprising the step of intramuscular injection to a cholinergic influenced muscle of a patient of a therapeutically effective amount of botulinum toxin type B, thereby reducing a lower back pain.

52. A method for treating post stroke spasticity pain, the method comprising the step of intramuscular injection to a cholinergic influenced muscle of a patient of a therapeutically effective amount of botulinum toxin type B, thereby reducing a post stroke spasticity pain.